Technical Memorandum

Comments on the OSHA Hexavalent Chromium Rulemaking for the Aerospace Industries Association

Prepared for

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Executive Summary

A technical analysis of the Occupational Safety and Health Administration's (OSHA's) risk assessment for hexavalent chromium [Cr(VI)], as it specifically applies to the aerospace industry, was conducted on behalf of the Aerospace Industries Association. Aerospace workers are exposed to Cr(VI) due primarily to priming and painting operations, and most exposures are to strontium chromate paint sprayed onto metal surfaces as a primer. Workers may also be exposed to chromic acid, which is used to treat the metal surface prior to priming. This analysis is focused on whether OSHA's risk assessment accurately predicts excess cancer risk due to current aerospace-industry exposures to Cr(VI). Several relevant issues are addressed.

The chromate production industry has been recognized for more than 50 years as having an increased risk of lung cancer, and virtually every study of this industry has observed an excess risk, some with more than twice the number of observed lung cancers as compared to that expected (e.g., Luippold et al. 2003). The lung cancer risk observed in this industry is not consistent with that observed in the aerospace industry, for which there are studies with very large cohorts and adequate follow-up periods, but no such relationship between Cr(VI) exposure and lung cancer has been demonstrated. OSHA's quantitative risk assessment analysis relies on the chromate production worker studies and the assumption that the exposure-response relationship for chromate production industry workers can be used to predict lung cancer risks among aerospace industry workers and all others. This is shown not to be the case. The epidemiology data for aerospace industry worker cohorts do not support a conclusion that there is a dose-response relationship between Cr(VI) exposure and lung cancer (Boice et al. 1999; Alexander et al. 1996), and OSHA's assessment of the lung cancer risk among aerospace workers overstates the findings (Boice et al. 1999) and inappropriately concludes there is a positive dose-response relationship, when in fact, an inverse relationship was reported by the original authors (Alexander et al. 1996). Moreover, the lung cancer mortality data and risk assessment based on the historical chromate production industry worker studies are not representative of the risks to aerospace industry workers exposed to Cr(VI). The quantitative cancer risk estimates should not be assumed applicable for aerospace industry workers.

Several key differences exist in the characteristics of Cr(VI) to which workers are exposed in the aerospace industry versus the chromate production industry. Differences include factors that affect bioavailability of chromium compounds, such as particle size and solubility, and exposure concentrations. These, ultimately, affect the potential toxicity of these compounds, particularly, the potential to cause lung cancer. Thus, it is not appropriate to conclude that quantitative exposure-response measures for lung cancer from the historical chromate production industry can be used to represent that for aerospace workers.

OSHA has assumed that there is a linear exposure-response relationship between high-level exposure in the chromate production industry and the low-level exposures experienced by aerospace workers. Such an assumption is based on the premise that short-term, high-level exposure poses the same risk as long-term, low-level exposure. This premise has not been proven. Moreover, the human body has physiological defense mechanisms that protect against damage due to low level exposure and/or toxicity of chemical agents, including Cr(VI). At low exposure levels, these defense mechanisms, which include metabolism, immune response and the repair of damaged cells, are most likely not overwhelmed. It is only when the exposures are high that the risk of toxicity from these chemicals increases. Exposures in the historical chromate production industry were much higher than those in the aerospace industry, which may explain the lack of evidence supporting an exposure-response relationship between Cr(VI) exposures and lung cancer among aerospace workers. Further, although it is nearly impossible to discern small increases in common diseases, such as lung cancer, at the low dose range using epidemiological data, among workers exposed to low levels of Cr(VI) in the Luippold et al. (2003) cohort—one of OSHA's featured studies—no excess in lung cancer was observed among workers with upper-bound exposures less than the current permissible exposure limit (PEL)—an average exposure of 27 $\mu g/m^3$, or those with a cumulative exposure of 1 mg-yrs/m^3, which equates to an occupational lifetime exposure of 22 $\mu g/m^3$ (Crump et al. 2003). Both of these exposure measures are slightly lower than average exposures to Cr(VI) in the aerospace industry worker studies.

While it is difficult to define the exposure levels at which the defense mechanisms are overwhelmed and an excess cancer risk is expected, the lack of scientific information to quantitatively define a sublinear dose-response should not be taken as evidence that it does not exist. Further, there is no evidence that low level exposure (approximately less than 20 $\mu g/m^3$) to Cr(VI) among aerospace workers poses a risk of lung cancer. Most notably Boice et al. did not observe significant excess in lung caner risk among more than 3,000 workers exposed to Cr(VI) in aircraft manufacture and repair, including those with exposure durations of more than 5 years, at average airborne concentrations that likely exceeded 15 $\mu g/m^3$.

The final issue addressed in these comments is the use of biological urinary monitoring to assess exposures to

Cr(VI) at the proposed Permissible Exposure Limit (PEL) of 1 $\mu g/m^3$. It is likely that such exposures would not raise the urinary Cr(VI) level sufficiently to distinguish it from background, and such a monitoring program would probably produce many false positives results or fail to detect low-level exposures when they do occur. These limitations are further compounded by the high intraindividual and interindividual variability in urinary chromium levels caused by dietary exposures, and other factors such as exercise and smoking. For these reasons, urinary biomonitoring should not be included in the proposed Cr(VI) rule.

Introduction

Exponent conducted a technical analysis of the risk assessment that the Occupational Safety and Health Administration (OSHA) prepared for hexavalent chromium [Cr(VI)] as it specifically applies to the aerospace industry on behalf of the Aerospace Industries Association. Aerospace workers are exposed to Cr(VI) due primarily to priming and painting operations, and most exposures are to strontium chromate paint sprayed onto metal surfaces as a primer. Workers may also be exposed to chromic acid, which is used to treat the metal surface prior to priming. Exponent's analysis focused on whether OSHA's risk assessment accurately predicts excess cancer risk due to current aerospace-industry exposures to Cr(VI).

Exponent's review addresses the following issues:

1. Differences between the exposure-response relationship observed among aerospace industry workers and that of the historical chromate production industry, which was used by OSHA to quantify the risk of lung cancer due to Cr(VI) exposure.

2. Comparison of Cr(VI) compounds and exposures from aerospace industry operations with those in the historical chromate production industry.

3. Evaluation of OSHA's assumption of linearity in the exposure-response relationship between very high-level occupational exposure in the historical (1940s to 1980s) chromate production industry and low-level exposures in the present-day aerospace industry.

4. The utility of biological urinary monitoring for Cr(VI) at exposures consistent with the proposed permissible exposure limit (PEL) of 1 μg/m^3.

Exposure-Response Relationships Observed Among Aerospace Industry Workers versus Historical Chromate Production Industry Workers

This review addresses whether OSHA's quantitative cancer risk assessment accurately predicts excess cancer risk due to Cr(VI) exposure among aerospace worker. There is considerable information available to evaluate the lung cancer risk among aerospace workers; however, much of it provides only qualitative measures of exposure, and there is co-exposure with solvents, which are typically the focus of the study. OSHA's review of the epidemiology, data associated with health effects among aerospace workers was relatively brief and focused on three studies (Boice et al. 1999; Alexander et al. 1996; Dalager et al. 1980). We have reviewed the findings of these studies in detail and discuss the findings of each with regard to Cr(VI) exposure and an increased risk of lung cancer.

While the two featured cohorts (Luippold et al. 2003 and Gibb et al. 2000) provide the best data available upon which to base an estimate of the exposure-response relationship between occupational exposure to Cr(VI) and an increased lung cancer risk, whether that relationship should be considered representative for aerospace industry workers, and others with Cr(VI) exposures, is an important question for this rule, for several reasons. One reason is that the cost-benefit analysis for aerospace industry workers rest on the assumption that the quantitative cancer risk estimates derived from studies of historical chromate production worker cohorts adequately describes that for aerospace workers.

There have been very large and well documented epidemiologic studies of aerospace industry workers exposed to Cr(VI), yet there is not sufficient evidence from the published literature to conclude that aerospace workers are at an increased risk of lung cancer due to Cr(VI) exposure. While these studies have limitations, and the vast majority do not provide quantitative exposure information, taken as a whole, the weight of evidence does not suggest that there is an elevated lung cancer risk among aerospace industry workers. By comparison, the chromate production industry has been recognized for more than 50 years as having an increased rate of lung cancer. A comparison between Cr(VI) exposures and the associated lung cancer risk observed among aerospace industry workers and that for the historical chromate production worker cohorts, which were used as the basis for OSHA's quantitative risk estimates, was conducted to ascertain reasons for observed dissimilarities in the exposure-response relationship in these industries. Factors that were evaluated included the forms of Cr(VI) to which aerospace industry workers are exposed, exposure concentrations, and other considerations such as particle size, bioavailability, and healthy worker effect.

We found that there are differences in the forms of Cr(VI) to which aerospace workers are (and have been) exposed as compared to Cr(VI) exposures in the chromate production industry cohort studies. Critical issues including particle size and exposure concentration may provide an explanation as to why elevated risks of lung cancer have not been found among aerospace industry workers exposed to Cr(VI). For these reasons, OSHA's quantitative lung cancer risk assessment, derived from historical chromate production worker "featured" cohorts, should not be considered characteristic of the risk among aerospace industry workers.

The epidemiology data for aerospace industry worker cohorts do not support a conclusion that there is a positive dose-response relationship between Cr(VI) exposure and lung cancer

Epidemiology studies of mortality among cohorts of aerospace workers have consistently demonstrated workers to be at no increased risk for lung cancer. Risk estimates for lung cancer tend to hover around 1.0, and no statistically significant increases have been identified in cohort recent studies of workers employed in aircraft manufacturing and repair. Lung cancer standardized mortality ratio (SMR) estimates have ranged from SMR = 0.80 ($p < 0.05$) (Garabrant et al. 1988), to SMR = 0.88, $p < 0.05$ (Boice et al. 1999), to SMR = 0.96 (Morgan et al. 1998) and SMR = 0.98 (Blair et al. 1998). Lung cancer risk has not been shown to increase significantly with increasing years employed in occupations where exposure to Cr(VI) is possible or probable (Boice et al. 1999). This is an important consideration because, while lacking Cr(VI) exposure data for most aerospace cohorts, most studies have involved large numbers of people and long follow-up periods.

OSHA identified three cohort studies of aerospace workers (Alexander et al. 1996; Boice et al. 1999; Dalager et al. 1980) that it believed were important for consideration in the assessment of the risk of respiratory system cancer associated with occupational exposure to Cr(VI) among aerospace industry workers. Of the available studies, OSHA selected Alexander et al. (1996) for the preliminary quantitative risk assessment.

Examination of Alexander et al. (1996) Aerospace Industry Worker Study

Alexander et al. (1996) conducted a retrospective cohort study that evaluated the potential association between Cr(VI) exposure and lung cancer in aerospace workers utilizing quantitative measures of exposure. Alexander et al. (1996) studied a cohort of 2,426 chromate-exposed aerospace workers employed for at least 6 months between 1974 and 1994, primarily in aircraft manufacturing divisions, and included spray painters, decorative painters, maintenance painters, paint mixers, paint-mixing attendants, maskers/sanders, polishers, chrome platers, and surface processors/tank tenders. This cohort was identified from computerized company work-history records, which is one of the strengths of this study that enabled the authors to estimate cumulative exposures. The cohort also included workers employed as early as 1940. Estimates of Cr(VI) exposure of the workers were based on industrial hygiene and work history records. In addition to classification based on cumulative chromate exposure, jobs were also classified according to source and species of chromates used. For example, the chromates used in painting operations are mainly of moderate or low solubility, such as zinc and strontium chromates, and the chromium compound used by platers and tank tenders is primarily chromium trioxide (chromic acid), which is highly soluble. To evaluate the effect of each type of chromate exposure on the risk of lung cancer, the cancer incidence was also evaluated with respect to the duration of employment as painters, platers, and tank tenders, and sanders/maskers and polishers. Standardized incidence (not mortality) ratios were calculated for lung cancer for the different sub-groups of exposure.

Not only did the authors obtain quantitative exposure information, they also attempted to adjust exposure for use of personal protective equipment and to classify exposure by the species of chromate associated with specific jobs. The authors identified cases of lung cancer using the Surveillance, Epidemiology and End Results (SEER) cancer registry and calculated standardized incidence ratios (SIRs) to estimate the risk of lung cancer relative to observed rates in the general population.

The median age of cohort members was 42 years, and the median years of follow-up were 8.9, neither of which may been sufficient to observe lung cancer incidence. The authors identified 15 cases of lung cancer from the study population. Compared to the general population, the overall risk of lung cancer in the cohort was actually *lower*, though not significantly (SIR = 0.8, 95% CI = 0.4, 1.3). The authors did not find evidence for a positive dose-response relationship between increasing exposure and incidence of lung cancer—risk did not increase with increasing cumulative exposure, both when considering exposure-period lags and when not. Workers with the greatest number of chromate-years exposed (time-weighted average (TWA) ≥184.8 $\mu g/m^3$) were actually at a *decreased* risk of lung cancer, though not significantly (SIR = 0.2, 95% CI = 0.1–1.1, without lag; SIR = 0.3, 95% CI = 0.01, 1.7, with 10-year lag). Increases in risk among subgroups of the cohort were not significant and were based on small numbers. The sander/polisher subcohort with greater than five cumulative years of employment had an elevated SIR = 2.7 (95% CI = 0.5, 7.8), but this observation was based on only three cases and could have occurred simply by chance. Similarly, the plater/surface processor/tank tender subcohort with greater than five cumulative years of employment had an elevated SIR = 1.9 (95% CI = 0.2, 6.9), but that was also based on only two cases. There were no significant excesses of risk identified for any subgroup of the cohort, by cumulative exposure or by decade of eligibility for the cohort.

At the end of the follow-up period, 26.2% of the cohort had been lost to follow-up. If loss to follow-up occurred differentially (i.e., if chromate-exposed workers who developed lung cancer were more likely to be lost to follow-up), then SIRs would be underestimates of actual risk. On the other hand, if chromate-exposed workers who developed lung cancer were less likely to be lost to follow-up than unexposed workers, then the SIRs would be overestimates of the true risk.

These limitations notwithstanding, and despite the fact that the observed dose-response was inverse, OSHA considered Alexander et al. as one of the studies upon which to base quantitative cancer risk estimates, and conducted an analysis using the published data. OSHA modeled a positive relationship, and concluded that the model results were sufficiently similar to that of the historical chromate production industry cohorts—specifically, the Luippold et al. and Gibb et al. cohorts—that the potency of Cr(VI) in the chromate production industry is predictive of that for aerospace industry workers.

Best estimates of cancer risk per exposure to Cr(VI) based on the Alexander cohort were not provided in the OSHA proposed rulemaking, but the upper 95% confidence interval (CI) on the risk was estimated to be 212 cases per 1000 workers, for a working lifetime exposure to Cr(VI) at the current OSHA PEL of 52 $\mu g/m^3$. OSHA attempted to draw parallels between the Alexander cohort and the Luippold and Gibb cohorts, by saying, "The 95 percent confidence intervals for the risk estimates from the Alexander cohort overlap those for equivalent risk estimates from both the Luippold and Gibb cohorts." Considering that both the featured cohorts had a strongly positive dose-response relationship between airborne exposure to Cr(VI) and lung cancer mortality, it is unjustified to say that the Alexander study was similar to both of these featured data sets based on the overlap of extremely wide confidence intervals for OSHA's modeled cancer risk estimates of the Alexander et al. and featured cohort data.

Standardized incidence ratios are summarized below for Alexander et al. (1996).

Table 1. Lung cancer incidence for aerospace workers with cumulative exposure and with no lag period and 10-year lag (from Alexander et al. 1996)

Cumulative Exposure to Cr(VI)	No Lag			10-year Lag		
μg-yrs/m^3	Obs	SIR	95%CI	Obs	SIR	95%CI
<9.8	7	1.5	0.6–3.2	10	1.2	0.6–2.3
0.98–49.2	2	0.4	0.1–1.5	0	0	0.0–1.1
49.3–184.7	5	1.1	0.3–2.5	4	0.9	0.2–2.3
>184.8	1	0.2	0.1–1.1	1	0.3	0.01–1.7

Obs – Observed number of cases of lung cancer
SIR – Standardized Incidence Ratio
95%CI – 95% confidence interval

Clearly, these data do not support a positive dose-response relationship. While both the study authors and OSHA correctly note that this study suffers from several limitations, the fact remains that no dose-response relationship could be determined between cumulative Cr(VI) exposure and lung cancer risk in this study. Interestingly, Alexander et al. discussed the observed differences in lung cancer risk with cumulative exposure to Cr(VI) in their study and that of other industries, noting that the lower solubility of Cr(VI) in paints may render paint-bound chromate less carcinogenic than pure chromate pigment.

The Alexander et al. (1996) cohort data should not be used for the quantitative preliminary risk assessment and other aerospace worker studies do not support a positive dose-response relationship between Cr(VI) exposure and lung cancer

As discussed in detail above, a positive dose-response relationship between Cr(VI) exposure and increased lung cancer risk was not observed in the Alexander et al. cohort of aerospace workers; rather, a negative relationship was observed in the study. It is misleading to use the results of this study for quantitative cancer risk assessment and predict a positive exposure-response to quantify risk. OSHA's risk assessment used a linear dose-response model to estimate a positive dose-response, where in fact, none exists, and offered quantitative estimates of increased lung cancer risks associated with Cr(VI) exposures. While it could be argued that follow-up was insufficient to observe a positive dose-response in the Alexander et al. cohort, this is not an adequate basis for including this study in the preliminary quantitative risk assessment analysis and applying a linear model to these data to predict a positive relationship between lung cancer risk and cumulative Cr(VI) exposure when a negative relationship was observed by the original researchers.

Examination of Boice et al. (1999) Aerospace Industry Worker Study

Of the three studies, the Boice cohort is the largest, best defined, most completely ascertained, and followed for the longest duration. Included in the cohort were 77,965 workers who accrued a total of 1.9 million person-years of observation during the 36-year follow-up period. Inclusion criteria were employment after December 1959 with at least 1 year of employment. Biases from selection or measurement of outcomes should not be problems in this study, because less than 1% of the cohort was lost to follow-up, and mortality ascertainment was 99% complete, with cause of death determined for over 98% of the cohort. Missing from the Boice et al. study were quantitative measurements of exposure to Cr(VI) and solvents, since exposure surveys were limited or absent in early years of the plant operations. However, the authors developed detailed methods to assess exposure, and used the length of time spent in jobs with potential exposure as their exposure metric.

Exposure of cohort members to compounds containing chromate occurred primarily while operating process equipment in lines of tanks used for plating or to protect metals from corrosion, or when using chromate-based primers or paints. Air-sampling data for the years 1978–1988 (as reported in Marano et al. 2000) indicate that the mean level of Cr(VI) measured was 15 $\mu g/m^3$ (median level = 1 $\mu g/m^3$). This estimate is for all Cr(VI) workers combined and may underestimate exposure, particularly to painters if the historical air sampling methods did not efficiently measure chromates of low solubility as compared to current techniques.

The authors found that, for workers routinely exposed to chromate, risk of lung cancer was as expected, with an SMR = 1.02 (95% CI = 0.82, 1.26) based on 87 observed cases among 3,634 workers routinely exposed (88,224 person-years). Even this subcohort of the Boice study is very large, larger than that of the Luippold et al. cohort the Gibb et al. cohorts combined in terms of total cohort members. Because the 95% confidence interval includes the null value, the 2% elevation in risk observed in Boice et al. is not statistically significant, indicating that workers routinely exposed to Cr(VI) did not have an increased risk of lung cancer compared to the general population at a level greater than chance. Furthermore, the authors also examined their findings in light of those from other studies as a consistency check. In accordance with other cohort studies of workers employed in aircraft manufacturing and repair, the authors demonstrate consistency between their estimate of lung cancer risk (SMR = 0.88, $p < 0.05$) and those from other studies SMR = 0.98 (Blair et al. 1998), 0.96 (Morgan et al. 1998), and 0.80 ($p < 0.05$) (Garabrant et al. 1988).

With a study sample as large as Boice et al., power should be very high to detect a statistically significant difference in risk, which emphasizes the importance of the lack of statistical significance of their findings. In other words, the study had the power to detect a statistically significant association, and the fact that so few were found that could not be attributed to the healthy worker effect, supports the conclusion that there is nothing to be found. However, the number of comparisons made in the Boice et al. study was numerous (over 820 total comparisons made), and therefore, significant increases or decreases in risk detected could be the result of the multiple comparisons, because by chance alone, 5% of the total comparisons [41 (0.05 x 820)] relative risks or trend statistics are expected to be significant. The authors did find several risk estimates for which observed mortality in the cohort or in a subcohort were significantly *lower* than what was expected for the general population. It is possible that the "healthy worker effect" is responsible for these observations.

Working cohorts tend to be "healthier" than the general population, a phenomenon that is termed the "healthy worker effect" (McMichael 1976). By virtue of the fact that working cohorts are employed, this suggests that they must be healthy enough to work, whereas the general population consists of both employed and non-employed people. Comparisons of occupational cohorts to the general population of which the cohorts are part thus need to take the "healthy worker effect" into consideration. Examinations of mortality ratios for all causes of death, comparing the working cohort to the general population, can provide an estimate of how "healthy" the occupational cohort is in relation to the general population. SMRs close to 100 indicate that the healthy worker effect is not very strong, while SMRs much less than 100 indicate a stronger healthy worker effect. In fact, for the Boice et al. cohort, the SMR for all causes of death for all the workers in the cohort was 0.83 (95% CI = 0.82, 0.84). The narrow confidence interval is indicative of the statistical power of the study.

The healthy worker effect is a lesser problem in studies that compare disease risks in subgroups of the working cohort that have all been adjusted to the general population or that report ratio measures of disease among subgroups of the working cohort, comparing one subgroup to another. The authors of Boice et al. made such comparisons, calculating risk ratios in internal cohort comparisons of workers exposed to chromate over potential years of exposure. They report that, compared to workers not exposed to chromate, lung cancer risk ratios were lower for workers *potentially* exposed to chromate for less than a year: RR = 0.90 (95% CI = 0.69, 1.16); for 1–4 years: RR = 1.02 (95% CI = 0.78, 1.33); and for five or more years: RR = 1.08 (95% CI = 0.75, 1.57). Not only does each of the confidence intervals for the risk estimates include the null value, indicating a lack of statistical significance of the estimate, but the confidence intervals all overlap, providing support that the risks associated with years of exposure are not different from each other. Statistical tests for trend indicated that there is no evidence for a trend of increasing risk of lung cancer with increasing years exposed to chromate ($p < 0.20$). OSHA seems to have "eye-balled" the estimates and felt confident accepting the slight and non-significant increases among risk estimates with overlapping confidence intervals as evidence of a "slight positive" trend. However, OSHA's interpretation is an overstatement of the finding and should be corrected in the final rule.

For the Cr(VI)-exposed subcohort of Boice et al,. no estimate of cancer risk was significantly elevated, nor were any estimates for specific occupations whose job duties involved potential exposure to compounds containing Cr(VI). Painters, an occupation of interest for their potential exposure to chromate-based primers or paints, had a slightly elevated risk of lung cancer (SMR = 1.11), but it was not at statistical significance (95% CI = 0.80, 1.51). Welders, an occupation of interest for their potential exposure to chrome plating, had a reduced risk of lung cancer (SMR = 0.85), also not at statistical significance (95% CI = 0.28, 1.98). The only statistically significantly elevated lung cancer risk among the entire cohort studied was among factory workers employed for durations of less than 10 years. This subgroup contains all occupations and all exposures, so that workers in this subgroup would include those exposed to chromate and to solvents, thus making this finding not specifically relevant to Cr(VI) exposure. In addition, taken in the context of the number of comparisons made, this significant elevation could also be explained by chance. Furthermore, despite the efforts made to assess exposure, the job metric approach is still a proxy for directly measured levels of exposure to Cr(VI) or other chemicals and carcinogens potentially relevant to the industry. Conclusions relating to risk of lung cancer were thus based on these proxy measures. Finally, the consistency in risk estimates among studies of aerospace workers adds support to the findings of Boice et al., which demonstrate no increased risk of lung cancer among aerospace workers as a group.

Examination of Dalager et al. (1980) Aerospace Industry Worker Study

OSHA also considered a study by Dalager et al. (1980) of workers in the aircraft manufacturing industry with specific occupations that could result in exposure to Cr(VI). The authors examined mortality among spray painters exposed to zinc chromate primer paints and among electroplaters exposed to chromic acid. The study included 977 male painters and 276 male electroplaters and a follow-up period of 18 years. Included in the study were only the workers for whom death certificates could be obtained, which included 90% of painters and 87% of electroplaters. The authors used proportionate mortality ratios (PMRs) as a measure of the difference between the observed and expected deaths in the cohort compared to the general population. No excess of deaths was observed among the electroplaters; therefore, no further analyses were done on this subgroup of workers.

PMR analyses of occupational cohorts suffer from two main weaknesses—the "healthy worker effect" and the "see-saw effect." Given that the occupational cohort is employed, they must be healthy enough to work, which means that comparing incidence or mortality of the cohort to the general population is likely to result in risk estimates that underestimate the true risk. In addition, because PMR is a measure of observed deaths due to a specific cause in the cohort compared to the proportion of deaths resulting from that cause in the general population, and the cohort is likely to be "healthier" than the general population, the "see-saw" effect may also occur, in which deficits in one cause of death necessarily result in corresponding increases in other causes of death. For example, lower rates of cardiovascular disease in the occupational cohort compared to the general population may result in an apparent "inflation" of cancer PMRs, because PMRs are calculated by equating observed numbers of deaths in the cohort to expected numbers of deaths from the general population.

The authors were aware of this observation in their data, with PMR <1 for cardiovascular disease and PMR significantly >1 for respiratory cancer. Thus, they calculated proportionate cancer mortality ratios (PCMR), taking only into account cancer deaths for selected sites. For this analysis, the PMR for respiratory cancer, while still elevated (PMR = 1.46) was reduced from the previous analysis and was not statistically significant. The authors also examined PCMR for respiratory cancer by length of interval between first employment and death. The significant excess of respiratory cancer was limited to painters with 20 or more years between first employment and death (PCMR = 1.04, $p < 0.01$).

There have been reports that painters smoke more heavily than the general male population, and the authors note that, in this cohort, cirrhosis was elevated, suggesting excess alcohol consumption, which is usually associated with smoking. In addition, there is the suggestion that the actual Cr(VI) exposure to painters included in the Dalager cohort may be higher than painters in other aircraft manufacturing cohorts, because the painters reportedly did not use any personal protective equipment when painting in booths. In addition, co-exposures to fiberglass particles and particles from grinding and sanding took place in the same shops where the painters worked. While the Dalager study is unique in that it reported a statistically significant increased rate of cancer mortality among aerospace workers, and none of the other studies reported an increased cancer risk, there are several limitations with this study design, and the overall weight of evidence from the aerospace industry indicates that there is not an excess lung cancer risk among aerospace workers exposed to Cr(VI).

Summary and Conclusion from Epidemiology Literature Review

There is not sufficient evidence from the published literature to conclude that aerospace workers are at an increased risk of lung cancer from their occupation-related exposure to Cr(VI).

Epidemiology studies of cohorts of aerospace workers have consistently demonstrated workers to be at no increased risk for lung cancer. Two of the three studies selected by OSHA for their risk assessment (Alexander et al. 1996; Boice et al. 1999) were unable to demonstrate significant increases in risk of lung cancer despite their size (Boice et al.), their use of incidence data (Alexander et al.), and their efforts to quantify exposure to Cr(VI) (Alexander et al.). Neither Boice et al. nor Alexander et al. found evidence for a significant dose-response relationship between increasing Cr(VI) exposure and risk of lung cancer which is consistent with other studies of aerospace workers (Garabrant e al. 1988; Morgan et al. 1998; Blair et al. 1998).

While the Dalager et al. study contributes information suggesting that there may be proportionately more deaths from respiratory cancer than other cancers among aerospace workers who paint as their primary occupation, there is some question as to whether doses in this cohort were comparable to those in others, because personal protective equipment was not used in the cohort. Finally, all three studies (Alexander et al., Boice et al., Dalager et al.) lack information about smoking history of the cohorts studied. Smoking is the most significant risk factor for lung cancer identified to date, and not controlling for it could result in positively biased estimates of risk.

Discussion of preliminary risk estimates from the two featured cohorts

It is clear that the data from the two featured cohorts, Gibb et al. (2000) and Luippold et al. (2003), offer the best information upon which to quantify the risk due to Cr(VI) exposure and an increased risk of lung cancer. However, both are representative of only one, relatively small industry. The substantial elevation of lung cancer risk among workers in the chromate production industry has been recognized for more than 50 years, and the association has been observed very consistently. Whether the risk due to exposures in this industry can be used to represent Cr(VI)-exposure-related risks in all others is questionable. It is important to recognize that, of the six studies used in the quantitative risk assessment, four are of chromate production industry workers, and the other two (Gérin et al. 1993 and Alexander et al. 1996) do not show an increased cancer risk with exposure to Cr(VI) among the worker populations studied—welders and aerospace workers.

OSHA's Risk Assessment of Gibb et al. 2000 — OSHA's contractor, Environ, applied several different mathematical models to estimate the risk of lung cancer associated with Cr(VI) exposure among workers of the Gibb et al. cohort, with a relatively high degree of consistency among the reported results. OSHA selected the results from the Relative Risk Model, using Baltimore City reference rates, and equal groupings of person years at risk. For these model parameters, the predicted risk for a 45-year occupational lifetime exposure to 1 $\mu g/m^3$ Cr(VI) is 9.1, with 95% confidence intervals of 4.0 to 14. These confidence intervals do not overlap those of the linear relative risk model of the Luippold et al. cohort. The corresponding best-estimate risk level from Luippold et al. (2003) is 2.1, with 95% CI ranging from 1.2 to 3.1.

NIOSH has conducted a complicated modeling analysis of cancer risk associated with Cr(VI) exposure (Park et al. 2004), and the original researchers of this cohort, Drs. Gibb and Lees, were coauthors on the published work. The advantage of the NIOSH/Park et al. risk assessment is that specific information regarding smoking was incorporated into the model. The results of the NIOSH/Park et al. assessment were similar to the many iterations investigated by Environ, with a lung cancer risk of 7.3 (95% CI: 2.7–14) for 45 years of occupational exposure to 1 $\mu g/m^3$. The NIOSH/Park et al. risk assessment results are most similar to Environ's linear Cox Model C2. Confidence intervals around the NIOSH/Park et al. risk estimates overlap those calculated by OSHA and Crump et al. (2003) for the Luippold et al. cohort. Further, as noted by OSHA, NIOSH/Park et al. found a significantly higher dose-response coefficient for nonwhite workers than for white workers, which appears to be evident from the Gibb et al. (2000) data. However, no significant race difference was found in Environ's Cox proportional hazards analysis. NIOSH/Park et al. reported an exposure-race interaction but concluded that there was no known biological basis for this finding; rather it was more plausibly related to misclassification of exposure or smoking status or simply due to chance.

While the risk estimates are very similar among the various approaches for modeling the Gibb et al. cohort data, consideration should be given to relying on the NIOSH/Park et al. analysis, which takes into account the smoking behavior of the cohort. Also, there is overlap between the risk estimates of NIOSH/Park et al. for the Gibb et al. cohort and that for the Luippold et al. cohort. It is recommended that OSHA use the NIOSH/Park et al. quantitative assessment of risk for the Gibb et al. cohort because it offers a more technically refined analysis of the risk.

Finally, it is important to recognize that the Gibb et al. cohort included a very large number of short-term workers, and because OSHA relied on a cumulative exposure metric for estimating the exposure-response relationship, the assumption is required that the lung cancer risk from short-term, high-level exposure is equivalent to that of long-term, low-level exposure of the same cumulative dose. As discussed in detail to follow, there are physiological defense mechanisms of the body are capable of detoxifying Cr(VI) such that OSHA's conclusion that the short-term high level dose is equivalent to a long-term high level dose is biologically implausible. While the Boice et al. study does not specify the exposure duration or cumulative exposures of the cohort of workers exposed specifically to Cr(VI), exposures were relatively low level (mean exposures of 15 $\mu g/m^3$) compared to the featured cohorts of Luippold et al. and Gibb et al. It is important to note that the longer-term, low-level exposures to the Boice et al. workers exposed to Cr(VI) did not result in an excess lung cancer risk. By comparison, a significant excess in lung cancer mortality was observed at relatively low levels in the Gibb et al. cohort; e.g., for cumulative exposures of 0 to 0.014 mg/m^3/yrs, the SMR was 1.50 with 95%CI: 1.18, 1.88) (Park et al. 2004). As is discussed in more detail in the next section, this is not comparable with that observed in the Boice et al. and Alexander et al. cohorts at similar cumulative exposure estimates/levels.

Comparison of Cr(VI) Compounds and Exposures from Aerospace Industry Operations to that of the Historical Chromate Production Industry

The aerospace industry, as part of its full-aircraft corrosion control program, uses several products that contain hexavalent chromium. Hence, there are several types of jobs in this industry that could potentially expose workers to Cr(VI). Cr(VI) is present in conversion coatings in the form of chromic acid, and in primers in the form of strontium chromate. Some of the job descriptions that potentially involve exposure to Cr(VI) include the application of conversion coat on the aircraft surfaces, especially with the use of spray equipment ("chromating"), the application of primer using spray equipment, and the abrasive blasting or "sanding" of already painted surfaces to remove the old paint or primer. Studies published by Carlton (2003a,b) provide exposure information for aerospace workers with these jobs in the U.S. Air Force. Mean TWA exposure to chromic acid during conversion coat treatment was 0.48 $\mu g/m^3$, which is below the American Council of Government Industrial Hygienists (ACGIH) threshold limit value (TLV) of 50 $\mu g/m^3$ for water-soluble Cr(VI) compounds, such as chromic acid (Carlton 2003a) and approximately equal to OSHA's proposed action level for Cr(VI) in the proposed rule (October 4, 2004). The mean TWA exposures to strontium chromate were 5.33 $\mu g/m^3$ during mechanical abrasion, and 83.8 $\mu g/m^3$ during primer application. These exposures far exceed the proposed PEL of 1 $\mu g/m^3$.

A review of current literature and relevant aerospace documents suggests that there are certain factors, such as particle size, solubility, and bioavailability of compounds used in the aerospace industry, which could affect toxicity and the potential cancer risk. This information may provide a scientific basis for explaining the lack of an increased lung cancer risk associated with Cr(VI) exposure in the aerospace industry. The following is a summary of factors that could affect the bioavailability of chromium compounds, and thus, toxicity and risk estimates.

Particle Size

As discussed in the Proposed Rule, upon inhalation, particles >5 μm in size are efficiently removed from the air stream in the extrathoracic region (page 59315). Particles that are between 2.5 and 5 μm are deposited in the tracheobronchial region and are removed by the mucociliary escalator. Only particles that are smaller than 2.5 μm are deposited in the alveolar region, and are therefore available for absorption into the bloodstream. Sabty-Daily et al. (2004) recently described the size distribution of paint spray aerosol particles containing Cr(VI) at an aerospace facility. The sampled paint products consisted of strontium chromate in an epoxy resin matrix. The size distribution of total chromium in particles in the paint aerosol had a Mass Median Aerodynamic Diameter (MMAD) of 7.5 μm, and that for particles containing Cr(VI) was 8.5 μm. Particles >10 μm made up, on average, 62% of the chromium and Cr(VI) mass in the paint aerosol. Particles >2 μm constituted 90% or more of the total chromium and Cr(VI) mass. The study also showed that about 72% of the Cr(VI) mass inhaled by a painter as particles from paint aerosol is deposited in the head airways region, and about 1.4% of the Cr(VI) mass may potentially deposit in the tracheobronchial region. This may be an important finding, because lung cancer among Cr(VI)-exposed workers is most typically bronchogenic carcinoma. Only 2% of the Cr(VI) mass is potentially deposited in the alveolar region (Sabty-Daily et al. 2004).

One of the limitations of this study was that a cut-off was set for the cascade impactors that were used as sampling devices. Two field studies were conducted in total. For the first field study, the cut-off was set for 10 μm, and for the second field study, the cut-off was 21 μm. Therefore, particles more than 10 and 21 μm could not be classified in these field studies. If larger sized particles (>10 to 21 μm) in the respective field studies, were also taken into consideration, it is likely that the proportion of Cr(VI) actually deposited in the tracheobrochial region of the lungs would be less than the author's estimate of 1.4% of total airborne Cr(VI).

LaPuma et al. (2001, 2002) described the chromate content in paint particles of varying sizes. They also used cascade impactors to collect and separate paint particles based on their aerodynamic diameter. The particles ranged from 0.7 to 34.1 μm, and the Cr(VI) content and the mass of dry paint in each particle size was determined. Particles less than 7 μm in size had disproportionately less Cr(VI) per mass of dry paint compared to larger particles. The chromium content per mass of dry paint decreased substantially with particle size. The smallest particles, which were about 0.7 μm in size, contained about 10% of the chromium content per mass of dry paint as the larger particles. Therefore, the smaller particles contain less chromium compared to larger particles, due to their smaller size (mass varies with the cube of the radius, i.e. if the radius is reduced to one-tenth, mass reduces to one-thousandth), and they also have less chromium content per mass of dry paint. These findings indicate that exposure to Cr(VI) particle sizes may differ between the painters and workers exposed in other industries. For example, the particles to which chrome platers are exposed are less likely to have a Cr(VI) bias as a function of particle size. This is because aerosols would be generated from a mixture involving a more soluble chromate salt in liquid form, which are different from the solid chromate particles in primer paints. Moreover, chromate emissions from spray painting may be overestimated, because larger particles are more likely to be trapped on an air filter compared to smaller particles. They contain disproportionately more chromium content per dry weight, but are less biologically relevant than the smaller particles.

Cassee et al. (2002) demonstrated the importance of particle size in lung toxicity after inhalation of cadmium particles of varying sizes. They used cadmium chloride aerosol to investigate the extent to which particles ranging in size from 33 to 1500 nm (each particle size at a concentration of 1 mg/m^3) are deposited in the lung, and the role of particle size in the pathophysiology of pulmonary effects in rats. They found that animals exposed to 33-nm particles showed the highest level of respiratory toxicity, followed by animals exposed to 637-nm particles, then to 170-nm particles. Animals exposed to 1495-nm particles were least susceptible to lung toxicity. The cadmium levels in the lungs of these groups of animals showed a similar relationship. This suggests that pulmonary toxicity is dependent on the size of particles, and the extent of deposition of these particles in the lungs. Because cadmium is similar to chromium in physical and chemical properties and is considered a pulmonary carcinogen, the findings of Cassee et al. are relevant for assessing toxicity to Cr(VI) as well.

In summary, the bioavailability of chromium compounds used in aerospace products is limited by particle size. This, in turn, affects the potential toxicity of these compounds and may be at least partially responsible for the lack of increased lung cancer risk in this industry as reported in many epidemiology studies.

While only very limited data are available on the particle size of airborne Cr(VI) in the historical chromate production industry, the data that do exist from the Luippold et al. cohort of workers indicates that the aerodynamic equivalent diameter (AED) of the dust was 1.7 μm (Proctor et al. 2003). In addition, there is intuitive evidence from the chromate production industry that the particle sizes were of the range to affect the tracheobronchial and alveolar regions of the lung, in that the cohorts experience high rates of lung cancer, an observation that has not been made among aerospace workers.

Cr(VI) Solubility in Strontium Chromate Paints and Review of Relevant Animal Studies

Strontium chromate is sparingly soluble in water at 1,200 mg/L at 25°C. Barium chromate and lead chromate, on the other hand, are even less soluble (barium, 4.4 mg/L; lead, 0.58 mg/L), and calcium chromate is much more soluble (163,000 mg/L) than the strontium salt. However, the calcium chromate compounds to which the workers of the historical chromate production industry were exposed from kiln dust and roast were likely far less soluble than pure calcium chromate.

There is still considerable debate regarding the carcinogenic potency of chromates in terms of the solubility of the various Cr(VI) compounds. On one hand, the animal implantation and/or instillation studies indicate that less or sparingly soluble chromates are more carcinogenic than the more soluble chromates, such as sodium dichromate. On the other hand, a comparison of the chromate production industry epidemiology studies (i.e., workers exposed to mostly water-soluble Cr(VI) with high rates of lung cancer) and those of the aerospace industry workers (i.e., exposed to less soluble forms of Cr(VI) but without high rates of lung cancer) suggest otherwise.

The studies by Levy et al (1986a,b) found an incidence of 43% and 62% bronchial carcinomas in rats with two different samples of strontium chromate, a sparingly soluble compound. Sodium dichromate, a highly water-soluble compound, did not cause a significant increase in tumor incidence. These studies were done using an intrabronchial pellet implantation system whereby pellets loaded with the test compound were surgically implanted into the bronchi of the animals. This is not a natural route of exposure to the chromium compounds, and if particle size is a significant factor in bioavailability of Cr(VI) in paints, this factor is not taken into account with this dosing approach.

During inhalation exposures in the workplace, the workers breathe a spray mist of the paint containing the chromium compound. This aerosol consists of varying sizes of particles with varying chromium content. Most of these particles are removed from the air stream at different locations in the tracheo-bronchio-pulmonary anatomy, depending on their size. The particles that are deposited in the bronchial or alveolar area are spread out over a large surface area. In contrast, implanting a pellet creates a high level of the compound in a very small, localized area, which overwhelms the body's defense mechanisms and results in an increased likelihood of tissue irritation and inflammation, as well as genetic damage. Moreover, when Cr(VI) particles are deposited in the lung, a portion is reduced to the trivalent form prior to absorption, which is not toxic compared to the hexavalent form. Implanting a pellet overwhelms the reductive capacity of the lung, so that Cr(VI) is not reduced to Cr(III) to the same extent.

Epidemiology studies involving workers in the chromate production industry indicate that it is the highly soluble compounds, such as sodium dichromate, that are carcinogenic to humans. Both of the featured data sets in the OSHA document bear testimony to this fact (Gibb et al. 2000; Luippold et al. 2003). On the other hand, there is a lack of clear evidence implicating less soluble compounds such as strontium and zinc chromates, in similar epidemiology studies involving aerospace workers. The solubility issue of chromates in terms of carcinogenic potential is far from resolved. Taking all of this available evidence into consideration, IARC (1990) drew the overall conclusion that all Cr(VI) compounds are carcinogenic. However, this conflicting evidence points to the fact that there is still a gap in our understanding of the pathophysiological mechanisms by which Cr(VI) produces lung carcinogenesis. Until the gap in our knowledge about this key issue is bridged, and seemingly conflicting data in animals and humans are reconciled, the animal implantation data should not be used as a basis to conclude that strontium chromate is more carcinogenic than soluble chromates when epidemiological evidence from the aerospace industry cohorts does not support that finding.

Finally, it is important to recognize that the historical chromate production workers were also exposed to sparingly soluble forms of calcium chromate that are generated in the production kilns (Proctor et al. 2003, 2004). These forms are expected to be complex calcium chromate molecules such as those observed from cement production in kilns. The roast of the chromate production industry may also include Cr(IV), and Cr(V) when not oxidized completely to the hexavalent state. Several studies of chromate production worker cohorts have demonstrated that the excess cancer risk is reduced when less lime is added to the roast mixture, reducing worker exposure to the sparingly soluble calcium chromate compounds (Luippold et al. 2003). Yet, the dose-response between water-soluble Cr(VI) measured in the Painesville and Baltimore chromate production plants and increased lung cancer risk is unequivocally positive. While there are clear differences in the forms of Cr(VI) to which aerospace industry workers and historical chromate production workers were exposed, the toxicological difference is unclear. The bioavailability of strontium chromate is likely to be lower than that of soluble forms of Cr(VI). For these reasons, it is not appropriate to consider the cancer risk associated with soluble Cr(VI) in the historical chromate production industry to be equivalent to that for aerospace workers and the risk associated with strontium chromate should not be considered greater than that for soluble chromates based on the results of animal implantation data in light of the far more relevant epidemiologic data.

Cr(VI) Exposure Concentrations

With respect to the comparability of Cr(VI) exposure between industries, we compared information on Cr(VI) exposure levels from the two chromate production cohort featured studies and that of the Alexander et al. and Boice et al. cohort studies.

For the Baltimore chromate production cohort (Gibb et al. cohort), cumulative exposure to Cr(VI) at the end of participants' working histories was estimated to range from 0 to 5.25 mg CrO_3/m^3/yr [1 to 2.7 mg Cr(VI)/m^3/yr], and while detailed information regarding exposure concentrations was not provided in this study, annual average exposures to Cr(VI) for workers of three job titles was presented in graphic form and was approximately 25 $\mu g/m^3$ on average, with upper-bound exposures of around 130 $\mu g/m^3$ (Gibb et al. 2000b). For the Painesville chromate production plant (Luippold et al. cohort), the average cumulative level of Cr(VI) was estimated to be 1.58 mg/m^3 /yr and ranged from 0.003 to 23 mg/m^3/yr. Average airborne concentrations in production areas of the plant were 720 $\mu g/m^3$ in the 1940s, 270 $\mu g/m^3$ from 1950 to 1964, and 39 $\mu g/m^3$ after 1964 (Proctor et al. 2004). Sixty percent of the cohort accumulated an estimated Cr(VI) exposure of $\leq$1.00 mg/m^3/yr, and among those workers, no increase in lung cancer risk was observed. This is equivalent to a 45-year working lifetime exposure of 22 $\mu g/m^3$.

Average exposures in the aerospace industry are notably lower than those of the chromate production worker cohorts used as focus studies. Exposures to Cr(VI) in the Boice et al. cohort, as described by Marano et al. (2000), averaged 15 $\mu g/m^3$ based on air monitoring data collected after 1977—17 years after exposure began Cumulative exposure estimates were not provided, but for 5 to 10 years of exposure to 15 $\mu g/m^3$, the cumulative exposure would have been 0.075 to 0.150 mg/m^3/yrs. This cumulative dose estimate for these longer term workers is likely an underestimate because 1) exposures in the earlier decades were likely higher than that measured in 1978 and thereafter because improved equipment typically results in greater efficiency and reduced exposures, and 2) the air monitoring methods may not have efficiently captured sparingly soluble Cr(VI) zinc and strontium chromate in the paints. In the Boice et al. cohort, there was a slight but non-statistically significant increase in cancer risk among workers who worked for more than 5 years.

Similarly, Alexander et al. provided only limited exposure information; cumulative exposure estimates ranged from <0.0098 to >0.184 mg-yrs/m^3, but no 8-hour time-weighted average (TWA) exposure estimates were provided in the published paper. Based on the range of cumulative exposures, it can be surmised that 8-hour TWA exposures were probably less than <20 $\mu g/m^3$.

Based on this rough comparison, it appears that exposures to Cr(VI) in the aerospace worker cohort studies are typically lower than that of the Luippold et al. featured cohort, and more consistent with, yet still somewhat lower than those of the Gibb et al. cohort. However, the lung cancer risks associated with Cr(VI) exposures in the aerospace worker cohorts is certainly much lower than as compared to those of the Gibb et al. cohort. While it is not possible to specifically identify corresponding cumulative exposure levels between the Gibb et al. and aerospace worker cohorts, it is interesting to note that SMRs at cumulative exposures ranging from 0.014 to 0.047 mg Cr(VI)-yrs/m^3 and 0.047 to 0.19 mg Cr(VI)-yrs/m^3 from Park et al. (2004) for the Gibb et al. cohort, there was a statistically significant increased cancer risk, with SMRs of 183 (95% CI: 103; 297) and 197 (95% CI: 106; 331), respectively. Study limitations hamper the comparison of SIRs from Alexander et al. (1996) to those reported by Park et al. for the Gibb cohort for the same dose; however, this comparison, *albeit* rough given the lack of specific exposure information in the Boice et al. study, would suggest that an increased risk of lung cancer should have been observed, if it existed in the Boice et al. subcohort exposed to Cr(VI) for periods of 1 to 4 years and >5 years. In conclusion, the lack of evidence of an increased lung cancer risk among aerospace workers exposed to Cr(VI), as compared to workers of the historical chromate production industry, may be related to a number of exposure conditions including particle size, solubility of Cr(VI) in respirable particles an/or exposure concentration. Regardless as to whether the basis for this difference can be clearly identified, it is important to recognize that there is no evidence that low level exposure (approximately less than 20 $\mu g/m^3$) to Cr(VI) among aerospace workers poses a risk of lung cancer. Most notably Boice et al. did not observe significant excess in lung caner risk among more than 3,000 workers exposed to Cr(VI) in aircraft manufacture and repair, including those with exposure durations of more than 5 years, at average airborne concentrations that likely exceeded 15 $\mu g/m^3$. Because of these factors and the observed lack of a dose-response between Cr(VI) exposures and lung cancer risk among aerospace workers, it is not reasonable to assume that the dose-response relationship quantified for chromate production workers is applicable to aerospace workers.

OSHA's Assumption of Linearity in the Exposure-Response Relationship Between High-Level Occupational Exposure in the Historical Chromate Production Industry and Low-Level Exposures in the Aerospace Industry

OSHA and the Toxicology Excellence for Risk Assessment (TERA) expert review panel offer a reasonable basis for selecting the linear dose-response model for estimating lung cancer risk associated with Cr(VI) exposures. One disadvantage of using the linear model that is not apparently addressed in OSHA's analysis is the dependence of the model on cancer risks at the highest exposure levels. Many linear extrapolations would fit data points on the low end of the dose-response, and to a large extent, the upper end of the exposure profile dictates the slope of the dose-response curve.

Examining the highest dose groups of the Luippold et al. and Gibb et al. cohorts is therefore warranted. In the Luippold et al. cohort, individuals exposed to the highest cumulative doses of Cr(VI) could typically be described as workers who started in the early years of operation (1940s), were exposed to the highest concentrations of Cr(VI), and had the greatest exposure to the high-lime production process and exposure to the sparingly soluble calcium chromates from the roast dust (Proctor et al. 2004). Exposure estimates from the 1940s in the Painesville plant averaged 720 $\mu g/m^3$. Thus, it is reasonable to conclude that the dose-response, at least for the Luippold et al. cohort, is largely driven by workers exposed to very high concentrations for significantly shorter time periods than the 45-year occupational lifetime that is used for OSHA's risk assessment. Also, exposures received by the early workers were the least certain, because they were based on the sparsest sampling events.

In 1950, a health survey of workers in the Painesville plant found that 65% experienced a perforated nasal septum, and 95% had ulcerated nasal mucosa (Miller 1950). These conditions are certainly not typical of current-day occupational exposures to Cr(VI) in the aerospace industry or any other industry in the United States. While it may be possible to estimate cancer risks from long-term occupational exposures to low levels of Cr(VI) from the cancer risk experienced under historical conditions, there are substantial uncertainties associated with doing so, and the biological relevance of such an extrapolation is highly questionable.

There are many reasons why there is not expected to be a linear dose-response relationship between short-term high dose exposure and long-term low dose exposure because the pathophysiological dynamics of the body are different in these two settings. Specifically, there are physiological defense mechanisms in place that protect the body from harm due to exposure to low-levels of toxicants which are overwhelmed by high-dose exposures. In general, these include physical barriers, such as the skin, metabolism (detoxification) of chemicals, immune system defense, and repair of damaged cells and cellular organelles. These defense mechanisms are also relevant for Cr(VI). In the lung, larger particles, containing the majority of the chromium mass as measured in an air sample, are removed from the air stream before they reach the smaller bronchi and the alveoli regions where they can damage the lung and increase the risk of carcinogenicity. In the bronchial and pulmonary regions of the lung, the mucociliary escalator removes inhaled particles, which are then swallowed, thus reducing chemical exposure via inhalation. Additionally, and specifically for Cr(VI), as discussed by OSHA in the proposed rule, reduction of the hexavalent form of chromium to the trivalent form by glutathione and ascorbate in the lung tissue and the phagocytosis and sequestration of particles by the pulmonary alveolar macrophages detoxifies Cr(VI) and reduces the carcinogenic hazard. Although absorption and reduction are competing reactions, the lung's capacity to reduce Cr(VI) to Cr(III) prior to absorption into cells is of limited capacity, thus more efficient at lower level exposure. Further, damaged cells and cell organelles in the lung are continuously repaired, such that some level of DNA damage associated with intracellular absorption Cr(VI), is expected to be repaired by enzymes in the nucleus (Berardi et al. 2004). Finally, if the preceding steps have been ineffective, cell cycle arrest and the removal of cells containing damaged DNA by the process of apoptosis may prevent the development of cancer (Berardi et al. 2004). All these "obstacles" to lung carcinogenesis provide the biological basis for a sublinear dose-response and the existence of a threshold below which there is expected to be no increased lung cancer risk.

Investigators studying the kinetics of the pulmonary clearance of particles observed a reduction in the rate of alveolar clearance when deposited lung burdens were high (Oberdorster et al. 1992). Interestingly, investigators evaluating inhaled particles in carcinogenesis bioassays observed excess tumors in animals that inhaled very high concentrations of apparently inert dusts, which were included in these studies as negative controls (Witschi and Last, as discussed in *Casarett and Doull's Principals of Toxicology*, 1995). Morrow (1992) developed the unified hypothesis that clearance mechanisms dependent on the activity of pulmonary alveolar macrophages can be overwhelmed by respirable dusts that are in far excess quantities than physiological loads. Consequently, these lung burdens persist for long periods and overwhelm natural defense mechanisms of the lung.

As exposures to Cr(VI) in the aerospace industry cohort studies of Alexander et al. and Boice et al. are lower than those of the historical chromate production industry studies used as the basis for quantitative risk estimates and factors such as particle size and solubility will may also affect the tissue dose to the lung, the lack of an observed increase in lung cancer risk in the aerospace studies may be a result of pulmonary detoxification mechanisms that are more effective at lower exposure concentrations. In which case, the risk of developing cancer is much lower in the current aerospace industry than in the historical chromate production industry

Finally, it should be acknowledged by OSHA that the use of a linear model to evaluate the relationship between occupational exposure and lung cancer risk is an assumption and that the models used to estimate lung cancer risk rely on the assumption that short-term, high-level exposure (e.g., 1 year of exposure to 45 $\mu g/m^3$) poses the same risk as low-level, long-term exposure (e.g., 45 years of exposure to 1 $\mu g/m^3$). While the options for quantitative risk assessment modeling approaches and selection of a dose-metric are admittedly limited, OSHA should discuss in greater detail the uncertainty associated with these assumptions and the biological plausibility supporting each. Where possible, quantitative measures of uncertainty and variability should be provided. Finally, the use of a linear model which predicts a positive dose-response relationship, where none is in fact observed in the original data (as in the case of OSHA's modeling of both the Gérin e al. and Alexander et al. cohorts) is not appropriate.

Utility of Cr(VI) Biological Urinary Monitoring at the Proposed PEL of 1 $\mu g/m^3$

Workers can incur occupational exposure to Cr(VI) through inhalation, dermal contact, and in small amounts, ingestion. The biologically significant pathway of exposure in the workplace, both in terms of extent and the effects on health, is via the inhalation route. OSHA has proposed a PEL of 1 $\mu g/m^3$ for the workplace, to be used as an 8-hour TWA (OSHA 2004). To assess exposures of workers to Cr(VI), OSHA has requested information regarding the use of urinary biomonitoring for chromium. The utility of biological monitoring of urinary chromium for assessing exposures to Cr(VI) at doses consistent with the proposed PEL of 1 $\mu g/m^3$ is examined in this comment.

After exposure to chromium, most (>50%) of the absorbed chromium (hexavalent and trivalent forms) in the body is eventually excreted in the urine as Cr(III), while a minor amount (<5%) undergoes excretion through the biliary tract and feces (OSHA 2004). Biological urinary monitoring has been used successfully in the past to assess exposures to high levels of Cr(VI) in the workplace (Krishna et al. 1975; Gao et al. 1994). However, various studies have shown that its utility is dubious when it comes to assessing low-level environmental and occupational exposures (Paustenbach et al. 1997). The usefulness and limitations of urinary biomonitoring for workplace exposures are discussed in this section.

The advantages of urinary monitoring include:

- Good correlation of chromium levels in urine with inhalation exposures to Cr(VI) at high exposure levels (Korallus et al. 1974a,b,c; Gylseth et al. 1977; Tola et al. 1977; Mutti et al. 1979; ATSDR 2000)
- Capable of detecting high-level, recent (within 48 hours) occupational exposure
- Easy sample collection
- Non-invasive.

Urinary biomonitoring of workers exposed to Cr(VI) has been used since the 1960s as a supplement to air monitoring (Krishna et al. 1975; Gao et al. 1994); however, while investigators have demonstrated a strong correlation between inhalation exposures to Cr(VI) in the workplace and urinary chromium levels, numerous human exposure studies have identified several confounding factors, which create doubt as to the usefulness of urinary biomonitoring (Gargas et al. 1994a,b; Finley et al. 1996; Kerger et al. 1997; Corbett et al. 1997; Paustenbach et al. 1996, 1997).

The main limitation of urinary biomonitoring is that low-level exposures, such as exposures at the proposed PEL or thereabout, may not increase the urinary chromium levels above background (0.24–1.8 $\mu g/L$) (IARC 1990; Iyengar and Woittiez 1988) and above the limit of detection (0.2 $\mu g/L$). In the past, air concentrations of 50 $\mu g/m^3$ in the workplace (welders) have resulted in a urinary chromium concentration of 40 $\mu g/L$ (Gylseth et al. 1977). Similarly, Tola et al. (1977) showed that similar exposures resulted in urinary chromium levels of 30 $\mu g/g$ creatinine, which is approximately equal to 40 $\mu g/L$ chromium, assuming 1.3 g/L of creatinine in the urine. These studies demonstrated a good correlation between inhalation exposures to chromium and urinary chromium levels in workers, but all of these studies examined exposures at least 50-times higher than the proposed PEL.

Low-level and high-level exposures ranging between 5 and 150 $\mu g/m^3$ have resulted in urinary chromium levels of 5.3 ±3.7 $\mu g/g$ creatinine and 33.3 ±6.9 $\mu g/g$ creatinine, respectively (Mutti et al. 1979). It is noteworthy that potassium dichromate is highly soluble in water and is thus easily absorbed and excreted in larger amounts. On the other hand, strontium chromate, the relevant chromium compound for the aerospace industry, is only slightly soluble in water and thus, would be expected to be absorbed and excreted more slowly. All of the above studies indicate that urinary chromium levels are increased above background only with high-level exposures of the workers. It is unlikely that exposures at the proposed PEL could be monitored reliably by a urinary biomonitoring program, and such a program would probably produce a high number of false-negative and false-positive results.

Factors that Influence the Biological Dose and the Amount Excreted in Urine

The amount of chromium that is absorbed through the lungs depends on the oxidation state of the chromium, the particle size and solubility of the chromium compounds, and the activity of the pulmonary alveolar macrophages and the levels of ascorbate and glutathione in the lung tissue (ATSDR 2000; OSHA 2004). Cr(VI) is absorbed to a greater extent than the trivalent form, because the hexavalent form can easily cross membranes. Particles greater than 5 μm in size are removed from the air stream in the extrathoracic region, while those that are bigger than 2.5 μm but less than 5 μm are deposited in the tracheobronchial tree. These particles are cleared by the mucociliary escalator and are eventually swallowed and absorbed through the gastrointestinal tract. Exposures at the proposed PEL of 1 μg/m^3 would result in a total exposure of 10 μg Cr(VI) per day, assuming 10-m^3 air intake per workday by a worker. However, of the 10 μg present in the intake air, not all of the Cr(VI) particles are absorbed. Of inhaled particles, only a proportion is retained in the lungs. From the amount of Cr(VI) retained in the lungs, a fraction is expected to be reduced to Cr(III), which has a lower capacity to cross biological membranes and hence, lower absorption rates (ATSDR 2000; OSHA 2004). The reduction of the Cr(VI) to Cr(III) depends on the levels of ascorbate and glutathione in the lung tissue, the epithelial lining fluid, and the activity of pulmonary alveolar macrophages.

The chromium compounds that are retained in the lungs and are not reduced to the trivalent form undergo absorption into the bloodstream. Depending on the solubility of the Cr(VI) compound, part of it is absorbed over time, and a remaining portion maybe phagocytosed by the alveolar macrophages. Intratracheal injection studies indicate that 53%–85% of Cr(VI) compounds (particle size <5 μm) are cleared from the lungs by absorption into the bloodstream or by mucociliary clearance; the rest remain in the lungs (ATSDR 2000). The time over which these compounds are absorbed may vary considerably (Bragt and van Dura 1983; ATSDR 2000). This is relevant for strontium, zinc, and lead chromate, which are either only slightly soluble in water or are insoluble, and may undergo slow absorption over time, thus reducing the biological dose entering the bloodstream.

The absorbed chromium in the blood is distributed into various compartments such as the erythrocytes, which take up Cr(VI) preferentially (Gray and Sterling 1950; Wiegand et al. 1988) and convert it to the trivalent form by combining with cellular proteins. In addition to blood, chromium is distributed into at least two other compartments that have slower elimination rates. Adipose and muscle tissue have elimination half-lives of a few days, and the liver and spleen retain chromium for months (OSHA 2004). Thus, it appears that, although the theoretical inhaled amount may be moderately high (~10 μg/day), a percentage of the total chromium particles inhaled is "lost" at each of the following steps: extent of retention in the lung, reduction in lung tissue to the trivalent form, phagocytosis by the alveolar macrophages, extent of absorption into the bloodstream, and distribution into various compartments of the body. This results in a lesser amount of chromium than the inhaled dose being eliminated in the urine in the next few hours or days, and the remainder being eliminated over a longer period of time. Therefore, the probability is lower of detecting high chromium levels in the urine and thus detecting exposure to high concentrations of hexavalent chromium.

ACGIH Biological Exposure Index

ACGIH has a threshold limit value (TLV-TWA) of 52 μg/m^3 for soluble Cr(VI). ACGIH has also estimated a biological exposure index (BEI) of 30 μg chromium/g creatinine in urine as equivalent to inhalation exposures at TLV dose. This means that the new proposed PEL of 1 μg/m^3 would be equivalent to about 0.6 μg chromium/g creatinine in the urine (or ~0.8 μg/L). This value lies within the range of background urinary excretion levels (0.24–1.8 μg/L) for chromium (e.g., without occupational exposures). Thus, exposures to levels near the PEL would not be distinguishable from background urinary chromium.

Limitations of Urinary Biomonitoring

Another factor that may prevent the clear interpretation of biomonitoring results is the high intraindividual and interindividual variability in the urinary chromium levels (Kerger et al. 1997; Gargas et al. 1994b; Paustenbach et al. 1997). The variability arises because chromium levels in the urine are affected by diet [for example, dietary chromium, both hexavalent and trivalent forms, and ascorbate, which reduces Cr(VI) to Cr(III)], smoking, and exercise (Gargas et al. 1994b; Paustenbach et al. 1997).

The half-life of chromium in the body is short ($t_{1/2}$ = 15–41 hours) (Tossavainen et al. 1980). This means that, to detect urinary chromium levels accurately, samples would have to be collected within 24–48 hours of the exposure event. For example, if high exposures occurred on a Monday, it would be unlikely that the urinary chromium levels would still be high enough to detect them on Friday (i.e., 4–5 half-lives later), especially considering the high and variable background.

The biological significance of urinary chromium levels has to be determined with caution, because high levels of Cr(III) in the urine could have resulted from exposure to either the hexavalent or trivalent form in workplaces where chemicals containing either form are present.

Finally, rigorous quality assurance and quality control (QA/QC) is required to obtain valid sample results. A stringent QA/QC program is necessary to prevent sample contamination, as well as to ensure consistency in other elements of the worker safety program such as medical surveillance (Anderson et al. 1993).

In conclusion, biomonitoring of urinary chromium levels maybe a useful tool to assess high-level exposures of workers to Cr(VI). However, exposures around the proposed PEL of 1 $\mu g/m^3$ will not result in urinary chromium levels that exceed background urinary Cr concentrations. The effect is that this tool will not only have lower specificity in its inability to distinguish Cr(VI) exposures from Cr(III) exposures, but will also have reduced sensitivity in detecting low-level exposures, even though they may be higher than the proposed PEL of 1 $\mu g/m^3$.

References

ATSDR. 2000. Toxicological profile of chromium. Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services, Atlanta, GA.

Alexander, B.H., H. Checkoway, L. Wechsler, et al. 1996. Lung cancer in chromate-exposed aerospace workers. Am. College Occup. Environ. Med. 38(12):1253–1258.

Anderson, R.A., T. Colton, J. Doull, J.G. Marks, R.G. Smith, G.M. Bruce, B.L. Finley, and D.J. Paustenbach. 1993. Designing a biological monitoring program to assess community exposure to chromium: Conclusions of an expert panel. J. Toxicol. Environ. Health 40(4):555–583.

Berardi, P., M. Russell, A. El-Osta, and K. Riabowol. 2004. Functional links between transcription, DNA repair and apoptosis. Cell Mol Life Sci. 61(17):2173-2180.

Blair, A., P. Hartge, P.A. Stewart, M. McAdams, J. Lubin. 1998. Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow up. Occup Environ Med. 55(3):161-171. Boice, J.D., D.E. Marano, J.P. Fryzek, C.J. Sadler, and J.K. McLaughlin. 1999. Mortality among aircraft manufacturing workers. Occup. Environ. Med. 56:581–597.

Bragt, P.C., and E.A. van Dura. 1983. Toxicokinetics of hexavalent chromium in the rat after intratracheal administration of chromates of different solubilities. Ann. Occup. Hyg. 27(3):315–322.

Carlton, G.N. 2003a. Hexavalent chromium exposures during full-aircraft corrosion control. AIHA J. 64(5):668–672.

Carlton, G.N. 2003b. The impact of a change to inhalable occupational exposure limits: Strontium chromate exposure in the U.S. Air Force. AIHA J. 64(3):306–311.

Cassee, F.R., H. Muijser, E. Duistermaat, J.J. Freijer, K.B. Geerse, J.C. Marijnissen, and J.H. Arts. 2002. Particle size-dependent total mass deposition in lungs determines inhalation toxicity of cadmium chloride aerosols in rats: Application of a multiple path dosimetry model. Arch. Toxicol. 76(5–6):277–286.

Corbett, G.E., B.L. Finley, D.J. Paustenbach, and B.D. Kerger. 1997. Systemic uptake of chromium in human volunteers following dermal contact with hexavalent chromium (22 mg/L). J. Expo. Anal. Environ. Epidemiol. 7(2):179–189.

Finley, B.L., P.K. Scott, R.L. Norton, M.L. Gargas, and D.J. Paustenbach. 1996. Urinary chromium concentrations in humans following ingestion of safe doses of hexavalent and trivalent chromium: Implications for biomonitoring. J. Toxicol. Environ. Health
48(5):479–499.

Gao, M., L.S. Levy, S.P. Faux, T.C. Aw, R.A. Braithwaite, and S.S. Brown. 1994. Use of molecular epidemiological techniques in a pilot study on workers exposed to chromium. Occup. Environ. Med. 51(10):663–668.

Garabrant, D.H., J. Held, B. Langholz, L. Bernstein. 1988. Mortality of aircraft manufacturing workers in southern California. Am J Ind Med. 13(6):683-693.

Gargas, M.L., R.L. Norton, D.J. Paustenbach, and B.L. Finley. 1994a. Urinary excretion of chromium by humans following ingestion of chromium picolinate: Implications for biomonitoring. Drug Metab. Dispos. 22(4):522–529.

Gargas, M.L., R.L. Norton, M.A. Harris, D.J. Paustenbach, and B.L. Finley. 1994b. Urinary excretion of chromium following ingestion of chromite-ore processing residues in humans: Implications for biomonitoring. Risk Anal. 14(6):1019–1024.

Gérin, M., A.C. Fletcher, C. Gray, R. Winkelmann, P. Boffetta, and L. Simonato. 1993. Development and use of a welding process exposure matrix in a historical prospective study of lung cancer risk in European welders. Int. J. Epidemiol. 22 Suppl 2:S22–S28.

Gibb, H.J., P.S. Lees, P.F. Pinsky, and B.C. Rooney. 2000. Lung cancer among workers in chromium chemical production. Am. J. Ind. Med. 38(2):115–126.

Gibb, H., P. Lees, P. Finsky, and B. Rooney. 2000b. Clinical findings of irritation among chromium chemical production workers. Am. J. Ind. Med. 38:127–131.

Gray, S.J., and K. Sterling. 1950. The tagging of red cells and plasma proteins with radioactive chromium. J. Clin. Invest. 29(12):1604–1613.

Gylseth, B., N. Gundersen, and S. Langard. 1977. Evaluation of chromium exposure based on a simplified method for urinary chromium determination. Scand. J. Work Environ. Health 3(1):28–31.

IARC. 1990. Monographs on the evaluation of carcinogenic risks to humans: Chromium, nickel and welding. World Health Organization, International Agency for Research on Cancer,

Volume 49.

Iyengar, V., and J. Woittiez. 1988. Trace elements in human clinical specimens: Evaluation of literature data to identify reference values. Clin. Chem. 34(3):474–481.
Kerger, B.D., B.L. Finley, G.E. Corbett, D.G. Dodge, and D.J. Paustenbach. 1997. Ingestion of chromium(VI) in drinking water by human volunteers: Absorption, distribution, and excretion of single and repeated doses. J. Toxicol. Environ. Health 50(1):67–95.
Korallus, U., H. Ehrlicher, and E. Wustefeld. 1974a. Trivalent chromium compounds: Results of a study in occupational medicine. Part 1. General Information; Technological Information; Investigations (German). Arb. Soc. Prev. 9:51–54.
Korallus, U., H. Ehrlicher, and E. Wustefeld. 1974b. Trivalent chromium compounds: Results of a study in occupational medicine. Part 2. Disease status analysis (German). Arb. Soc. Prev. 9:76–79.
Korallus, U., H. Ehrlicher, and E. Wustefeld. 1974c. Trivalent chromium compounds: Results of a study in occupational medicine. Part 3. Clinical studies (German). Arb. Soc. Prev. 9:248–252.
Krishna, G. J.S. Mathur, S.K. Mehrotra, S.N. Sharma, and M.M. Alamkhan. 1975. Blood and urine concentration of chrome in chrome industry workers. Indian J. Med. Res.
63(9):1357–1362.
LaPuma P.T., and B.S. Rhodes. 2002. Chromate content versus particle size for aircraft paints. Regul. Toxicol. Pharmacol. 36(3):318–324.
LaPuma, P.T., J.M. Fox, and E.C. Kimmel. 2001. Chromate concentration bias in primer paint particles. Regul. Toxicol. Pharmacol. 33(3):343–349.
Levy, L.S., P.A. Martin, and P.L. Bidstrup. 1986. Investigation of the potential carcinogenicity of a range of chromium containing materials on rat lung. Br. J. Ind. Med. 43(4):243–256.
Levy, L.S., and S. Venitt. 1986. Carcinogenicity and mutagenicity of chromium compounds: The association between bronchial metaplasia and neoplasia. Carcinogenesis 7(5):831–835.
Luippold, R.S., K.A. Mundt, R.P. Austin, E. Liebig, J. Panko, C. Crump, K. Crump, and D. Proctor. 2003. Lung cancer mortality among chromate production workers. Occup. Environ. Med. 60(6):451–457.
Marano, D.E., J.D. Boice, J.P. Fryzek, J.A. Morrison, C.J. Sadler, and J.K. McLaughlin. 2000. Exposure assessment for a large epidemiological study of aircraft manufacturing workers. Appl. Occup. Environ. Hyg. 15:644–656.
McMichael, A.J.. 1976. Standardized mortality ratios and the "healthy worker effect": Scratching beneath the surface. J. Occup. Med. 18(3):165–168.
Miller, J.S. 1950. Effect of chromates on nose, throat, and ear. AMA Arch. Otolaryngol. 172–178.
Morgan, RW, Zhao, K, Kelsh, MA and S. Heringer. 1998 Mortality of aerospace workers exposed to trichloroethylene. Epidemiology. 9:424-431.
Morrow, P.E. 1992. Dust overloading of the lungs: update and appraisal. Toxicol Appl Pharmacol. 113(1):1-12.
Mutti, A., A. Cavatorta, C. Pedroni, A. Borghi, C. Giaroli, and I. Franchini. 1979. The role of chromium accumulation in the relationship between airborne and urinary chromium in welders. Int. Arch. Occup. Environ. Health 43(2):123–133.
Oberdorster, G., J. Ferin, P.E. Morrow. 1992. Volumetric loading of alveolar macrophages (AM): a possible basis for diminished AM-mediated particle clearance. Exp Lung Res. 18(1):87-104.
OSHA. 2004. Occupational exposure to hexavalent chromium; proposed rule. U.S. Occupational Safety and Health Administration. October 4.
Park, R.M., J.F. Bena, L.T. Stayner, R.J. Smith, H.J. Gibb, and P.S. Lees. 2004. Hexavalent chromium and lung cancer in the chromate industry: A quantitative risk assessment. Risk Anal. 24(5):1099–1108.
Paustenbach, D.J., J.M. Panko, M.M. Fredrick, B.L. Finley, and D.M. Proctor. 1997. Urinary chromium as a biological marker of environmental exposure: What are the limitations? Regul. Toxicol. Pharmacol. 26(1 Pt 2):S23–34.
Paustenbach, D.J., S.M. Hays, B.A. Brien, D.G. Dodge, and B.D. Kerger. 1996. Observation of steady state in blood and urine following human ingestion of hexavalent chromium in drinking water. J. Toxicol. Environ. Health 49(5):453–461.
Proctor, D.M., J.P. Panko, E.W. Liebig, and D.J. Paustenbach. 2004. Estimating historical occupational exposure to airborne hexavalent chromium in a chromate production plant: 1940–1971. JOEH 1:752–767.
Proctor, D.M., J. Panko, E. Liebig, et al. 2003. Workplace airborne hexavalent chromium concentrations for the Painesville, Ohio Chromate Production Plant (1943–1971). Appl. Occup. Environ. Hyg. J. 18(6):430–449.
Sabty-Daily, R.A., P.A. Harris, W.C. Hinds, and J.R. Froines. 2004. Size distribution and speciation of chromium

in paint spray aerosol at an aerospace facility. Ann. Occup. Hyg. 10 (in press). [Epub ahead of print: Dec 10, 2004]
Sanlioglu, A.D., C. Aydin, H. Bozcuk, E. Terzioglu, and S. Sanlioglu. 2004. Fundamental principals of tumor necrosis factor-alpha gene therapy approach and implications for patients with lung carcinoma. Lung Cancer. 44(2):199-211.
Sjögren, B., A. Gustavsson, and L. Hedstrom. 1987. Mortality in two cohorts of welders exposed to high- and low-levels of hexavalent chromium. Scand. J. Work Environ. Health 13(3):247–251.
Tola, S., J. Kilpio, M. Virtamo, and K. Haapa. 1977. Urinary chromium as an indicator of the exposure of welders to chromium. Scand. J. Work Environ. Health 3(4):192–202.
Tossavainen, A., M. Nurminen, P. Mutanen, and S. Tola. 1980. Application of mathematical modelling for assessing the biological half-times of chromium and nickel in field studies. Br. J. Ind. Med. 37(3):285–291.
Wiegand, H.J., H. Ottenwalder, and H.M. Bolt. 1988. Recent advances in biological monitoring of hexavalent chromium compounds. Sci. Total Environ. 71(3):309–315.
Witschi, H.R. and J.A. Last. 1995. Toxic Responses of the Respiratory System. In Casarett and Doull's Toxicology, The Basic Science of Poisons. McGraw Hill Companies, Inc.